# Clinical review

# Acute pancreatitis

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## Introduction

More than a century after its comprehensive description by Reginald Fitz,[1] acute pancreatitis remains a common disorder with potentially devastating consequences. Although most episodes are mild and self limited, up to a fifth of patients develop a severe attack that can be fatal.[2] The overall mortality of acute pancreatitis remains 5-10%[3–5] and may increase to 35% or higher if complications develop.[5] The disease's course in a patient with acute pancreatitis is not always apparent at presentation; some patients get worse before they get better.

## Methods

This overview was prepared from a continuous review of publications in gastroenterology and general medicine journals, supplemented by a formal Medline search and review of the most recent articles on pancreatitis. Reviews have been supplemented by original papers that include important recent developments. This review also reflects almost two decades of personal clinical experience and research related to pancreatitis by one of us (JB).

## Definition

Acute pancreatitis is an acute inflammatory process of the pancreas that can involve peripancreatic tissues or remote organ systems, or both.[6] It may occur as an isolated attack or recur in distinct episodes with reversion to normal histology between attacks. By definition, acute pancreatitis is reversible; it is distinguished from chronic pancreatitis by the absence of continuing inflammation, irreversible structural changes, and permanent impairment of exocrine and endocrine pancreatic function. As the diagnosis of acute pancreatitis is usually made on clinical grounds and pancreatic tissue is rarely available, it can be difficult to distinguish between acute and chronic pancreatitis in the individual case.

The most commonly used classification system for acute pancreatitis distinguishes between mild and severe disease.[6] Severe disease is characterised by organ failure or local complications such as necrosis, pseudocysts, or fistulae. Scoring systems use prognostic signs to stratify patients and help in the early recognition of patients with a high probability of developing severe pancreatitis (see below).

## Summary points

Acute pancreatitis is a potentially fatal disease with a mortality of 5-10%

80% of all cases are caused by gallstones or alcohol

Patients with acute pancreatitis often get worse before they get better and need close monitoring and frequent reassessment

Computed tomography has an important role in the diagnosis of acute pancreatitis as well as the detection of complications such as pseudocysts and necrosis

Specific treatment for most cases of acute pancreatitis is still lacking; supportive care includes intravenous fluids, parenteral analgesia, and attention to the patient's nutritional status

Antibiotics should be reserved for patients with documented infection or severe necrotising pancreatitis

## Pathophysiology

The early stages of acute pancreatitis are characterised by interstitial oedema within the pancreatic parenchyma and necrosis of peripancreatic fat. The disease may progress to coagulation necrosis of glandular elements and the surrounding fatty tissue, a condition described as necrotising pancreatitis.

Premature activation of pancreatic enzymes is the central event in the pathogenesis of acute pancreatitis.[7] Once activated, trypsin can activate many other enzymes, including kallikrein, phospholipase A2, and elastase.[7] This leads to autodigestion of pancreatic tissue as well as systemic effects from circulating enzymes causing vasodilation, increased capillary permeability with leaking of fluid into the third space, and disseminated intravascular coagulation. In the most severe cases, the result is circulatory collapse, renal insufficiency, and respiratory failure. Despite extensive research, the mechanism(s) that trigger the initial sequence of enzymatic activations remain

incompletely understood. Factors that can initiate this process include acute obstruction of the pancreatic duct, exposure to toxins and venoms, and ischaemia.[7]

Once initiated, the biochemical and pathophysiological processes resulting in acute pancreatitis cannot be inhibited or reversed. Treatments aimed at halting the cycle of pancreatic autodigestion (glucagon, somatostatin, anticholinergics) have generally been disappointing. A recent meta-analysis of six trials using somatostatin showed a small benefit,[8] but further research is needed before this drug should be routinely considered. Efforts to prevent acute pancreatitis in well defined subgroups of patients (such as those undergoing endoscopic retrograde cholangiopancreatography (ERCP)) have yielded more encouraging results. A recent European trial using intravenous infusion of gabexate (not yet available in the United States) to prevent post-ERCP pancreatitis found this drug to be efficacious, although cumbersome to administer.[9]

For a more detailed discussion of the pathophysiology of acute pancreatitis, interested readers are referred to recent reviews.[7 10]

## Conditions associated with acute pancreatitis

Calculi in the common bile duct (choledocholithiasis) and alcohol account for 80% of cases of acute pancreatitis. Many other conditions are associated with the disease (box).

Identifying the underlying cause is important: the risk of recurrence may be predicted, and eliminating the underlying cause (discontinuing a drug, for example) may prevent further attacks. In specific instances, such as severe pancreatitis with cholangitis due to impaction of a gallstone at the ampulla of Vater (fig 1), identifying the problem and dealing with it immediately (by ERCP and sphincterotomy for biliary decompression) may favourably influence the course of the disease.[11 12]

In about 10% of cases of acute pancreatitis, no underlying cause can be identified (idiopathic pancreatitis). Recently, two prospective studies of patients with idiopathic pancreatitis found that about two thirds had
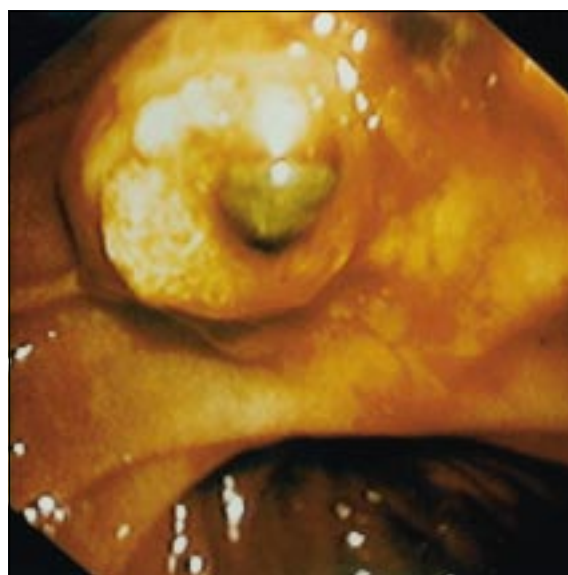


**Fig 1** Endoscopic view of impacted gall stone at ampulla of Vater

| Conditions associated with acute pancreatitis[15] | |
| --- | --- |
| Cholelithiasis, choledocholithiasis, or biliary microlithiasis | Vasculitis |
| Ethanol misuse | Ischaemia or embolism |
| Drugs (see other box) | Pregnancy |
| Trauma | Organ transplantation |
| Major abdominal surgery | End stage renal failure |
| Cardiopulmonary bypass | Mycoplasma infection |
| Hypercalcaemia | Viral infection (mumps, coxsackie B, HIV, etc) |
| Hyperlipidaemia | Venoms (scorpion bite, certain spider bites) |
| Penetrating gastric or duodenal ulcer | |
| Pancreatic tumours | Intraductal parasites (ascariasis, for example) |
| Pancreas divisum* | |
| Familial pancreatitis | Idiopathic causes |

*A normal variant in 7%-8% of white populations

small gallstones and biliary sludge at ERCP; these patients responded favourably to endoscopic sphincterotomy or cholecystectomy, or both.[13 14]

ERCP is indicated in patients with recurrent episodes of acute pancreatitis of undetermined aetiology to look for biliary stones (including microlithiasis), anomalous or pathological biliary or pancreatic anatomy (such as choledochocele), and unsuspected obstructing lesions of the ampulla of Vater. Cross sectional imaging of the liver, gall bladder, biliary tree, and pancreas by transabdominal ultrasound, computed tomography, and magnetic resonance imaging are all helpful in identifying specific causes of pancreatitis. Not all patients who have an attack of pancreatitis require ERCP.

## Clinical presentation

The hallmark of acute pancreatitis is a continuous, boring epigastric pain. It is usually poorly localised, is often worse in the supine position, and radiates to the back in about 50% of patients. In contrast to the often abrupt onset of pain that accompanies perforation of an abdominal viscus, the pain increases in severity to a peak in 30 to 60 minutes, then remains steady for many hours or days. Localised epigastric tenderness can be intense, but signs of peritoneal irritation such as rebound tenderness are typically absent on initial presentation, consistent with the retroperitoneal location of the pancreas. Acute ischaemia of the bowel should be considered in the differential diagnosis.

| Drugs associated with pancreatitis[7] | |
| --- | --- |
| *Definite association:* | • Sulphasalazine |
| • Azathioprine | • Paracetamol overdose |
| • 6-Mercaptopurine | • Ergotamine overdose |
| • Asparaginase | |
| • Pentamidine | *Possible association:* |
| • Didanosine | • Corticosteroids |
| | • Cyclosporin |
| *Probable association:* | • Metronidazole |
| • Valproic acid | • Erythromycin |
| • Frusemide | • Piroxicam |
| • Hydrochlorothiazide | • Cimetidine |
| • Sulphonamides | • Metolazone |
| • Tetracyclines | • Methyldopa |
| • Oestrogens | • 5'-Aminosalicylic acid |

This list is not exhaustive; other drugs may be associated with pancreatitis in individual cases.

Most patients have nausea and vomiting; if severe, this is an indication for continuous or periodic aspiration of stomach contents. A nasogastric tube is not necessary in mild pancreatitis. Vomiting and massive third space losses can rapidly lead to depletion of intravascular volume. The patient's urine output should be documented accurately (which may require placing a urinary catheter) and signs of dehydration treated promptly with intravenous fluids. A low grade fever (37.7-38.3°C) without other evidence of an ongoing infectious process, pancreatitis is not an indication for empirical treatment with antibiotics, but the patient must be watched for signs of systemic infection.

Abdominal distension is common in acute pancreatitis. Leakage of fluid into the retroperitoneum—the body's effort to dilute pancreatic enzymes and thereby contain the ravages of autodigestion—causes the abdominal contents to be pushed forward. This protrusion of abdominal contents, exacerbated by loops of bowel filled by gas and fluid from the almost inevitable small bowel ileus, may grossly distend the abdomen. The almost universal ileus of all but mild pancreatitis may be exacerbated by the narcotic analgesia needed to treat the intense pain of this condition. Evidence of retroperitoneal haemorrhage, specifically periumbilical bruising (Cullen's sign) and flank bruising (Grey-Turner's sign) is rare but should be sought as a prognostic indicator.

Respiratory problems are common in acute pancreatitis. The tendency to hypoventilation may be exacerbated by basal pleural effusions and atelectasis. The most severe respiratory complication of acute pancreatitis, adult respiratory distress syndrome, is rare but potentially fatal. These patients usually require ventilatory support. In a recent British study of acute pancreatitis with fatal outcome, respiratory failure was more common than infection or sepsis.[5]

Hypocalcaemia is common (due to saponification of fat) but tetany (due to loss of ionised calcium) is rare. Hypocalcaemia is a negative prognostic factor (see below); significant hypocalcaemia (after correction for serum concentration of albumin, which is also often low) should be treated by intravenous replacement.

## Laboratory diagnosis

Serum amylase is the most practical initial laboratory test for the diagnosis of acute pancreatitis. Results are usually available within 60 minutes. However, this serological test has low specificity (less than 70%) when the upper limit of the normal range is used as the cutoff value,[7] and other conditions cause rises in serum amylase (perforated viscus, renal insufficiency, ischemic bowel, salivary gland inflammation and tumours, etc). Amylase is a small molecule that is rapidly cleared by the kidneys, so abnormally high concentrations of serum amylase in acute pancreatitis may be short lived.

Because of its greater specificity, serum lipase is the test of choice if it can be measured with the same rapidity as amylase.[16] The simultaneous determination of amylase and lipase offers a sensitivity and specificity of 90-95% for detecting acute pancreatitis in patients presenting with acute abdominal pain.[17] Serum lipase takes longer to clear from the bloodstream so it is a more useful "historical" indicator of pancreatitis than serum amylase (fig 2). A three minute urinary dipstick
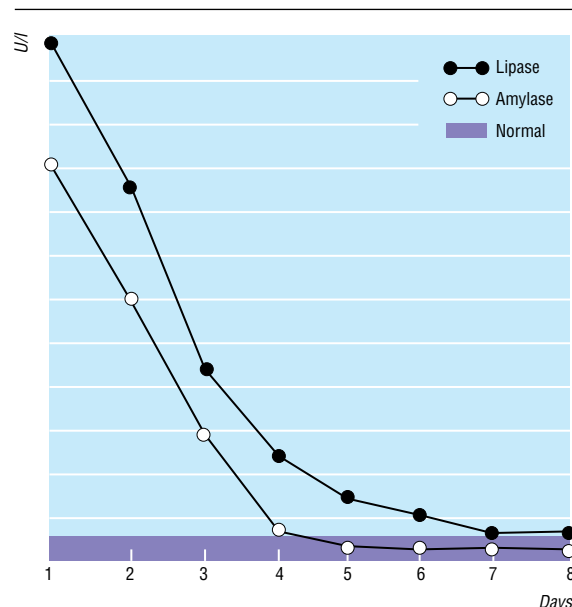


**Fig 2** Time course of increase in amylase and lipase in acute pancreatitis. Modified from Ventrucci et al[18]



**Fig 3** Transabdominal ultrasound revealing gall stones (with characteristic acoustic shadowing) in a patient with acute pancreatitis

test for trypsinogen-2 is showing promise as a screening tool.[19]

Distinguishing between the two most common aetiologies of acute pancreatitis, gall stones and alcohol, has important implications for treatment. Isolated mild hyperbilirubinaemia is a nonspecific sign.[15] Alanine aminotransferase concentration >80 IU/l is very specific for gallstone pancreatitis, but only 50% sensitive.[20] Ultrasonography (fig 3), the test of choice for diagnosis of common duct stones in patients with acute cholecystitis, has its limitations in patients with acute pancreatitis.[15] Overlying bowel gas from a coexistent ileus frequently obscures the area of interest, and the sensitivity of ultrasound for detecting pancreatic necrosis is low. Biliary pancreatitis is best distinguished from alcoholic pancreatitis by a combination of biochemical measurements (bilirubin, alanine aminotransferase) and transabdominal ultrasound (diagnostic accuracy of up to 98%).[21]

Contrast enhanced computed tomography is the most useful imaging method in patients with moderate or severe acute pancreatitis. Scans are normal in 15-30% of patients with mild pancreatitis. In more severe cases, a contrast enhanced CT scan may show pancreatic necrosis (fig 4), pseudocysts, and intra-

abdominal fluid. However, not every patient with acute pancreatitis needs a scan. This imaging study should be considered if the initial diagnosis is in doubt; if severe pancreatitis is suspected, a scan obtained within the first 3-4 days has an accuracy of over 90% for detecting pancreatic necrosis.[22] If patients fail to improve and have pain, fever, or leucocytosis, a scan will identify necrosis and detect pseudocysts or other fluid collections.

## Prognostic indicators

Patients likely to have a severe attack are best managed in an intensive care unit. Numerous standardised tools for assessment have been developed to identify patients at risk. Ranson's criteria remain the most commonly used (box).[23] The five initial criteria assess the severity of the acute inflammatory process, whereas the six criteria measured at 48 hours determine the systemic effects of circulating enzymes and toxins. The presence of three or more Ranson's signs usually indicates severe pancreatitis. Mortality increases with the number of Ranson's signs (patients with ≤2 criteria, 3-4 criteria, or ≥5 criteria have death rates of <1%, 16%, and >40%, respectively). A limitation of the Ranson system (and of other commonly used scoring systems, such as the Glasgow criteria[24]) is the need to wait 48 hours to obtain a complete assessment. The APACHE II system allows a more rapid determination of prognosis but is more cumbersome to use.[25]



**Fig 4** Computed tomography of severe necrotising pancreatitis during rapid intravenous bolus injection of contrast material. (a) Closed arrow shows an island of normally enhancing parenchyma in the pancreatic head adjacent to non-perfused necrotic areas; open arrows show fluid collections in the prerenal spaces; (b) Arrows show necrosis (lack of contrast enhancement) in most of the pancreatic body and tail

**Ranson's criteria of severity of acute pancreatitis[23]**

*On admission:*
- Age >55 years
- White blood count >16 000/mm³
- Glucose >11.0 mmol/l
- Lactate dehydrogenase >350 IU/l
- Aspartate aminotransferase >250 U/l

*During initial 48 hours:*
- Packed cell volume decrease >10%
- Blood urea nitrogen increase >1.8 mmol/l
- Calcium <2 mmol/l
- Partial pressure of oxygen <60 mm Hg
- Base deficit >4 mmol/l
- Fluid sequestration >6 l

## Treatment

Patients with acute pancreatitis should be given nothing by mouth, intravenous hydration, and frequent parenteral analgesia. Vigorous intravenous rehydration is essential to avoid prerenal azotaemia. Patients with an ileus should fast until their bowel sounds start to return. Patients with a prolonged ileus (>5-7 days) and those with persistent nausea or vomiting or with pain on eating or drinking despite apparent improvement in bowel function require enteral or parenteral nutrition. Delay in providing nutritional support may slow recovery and prejudice the outcome of major surgery. Enteral feeding beyond the ligament of Treitz via a long nasoenteral tube may be preferable to parenteral nutrition.

Pain in acute pancreatitis often requires narcotic analgesia. Pethidine has been recommended over morphine to avoid inducing spasm of the sphincter of Oddi, but its clinical relevance is not known. Care must be taken with pethidine, as its active metabolite, normeperidine, may accumulate with toxic effects.

Do patients with pancreatitis need antibiotics? Pancreatic infection in severe acute pancreatitis results from bacterial translocation and colonisation of necrotic tissue. Prophylactic antibiotics may reduce sepsis in cases of pancreatic necrosis.[26] Recent studies suggest that prophylactic antibiotics should be mandatory in patients predicted to develop severe pancreatitis.[27]

The need for the patient to avoid factors that may have caused pancreatitis, such as alcohol or certain drugs, is self evident. If the acute episode was thought to be precipitated by hyperlipidaemia, treatment should prevent recurrences. Endoscopic detection and extraction of common bile duct stones by ERCP is indicated in the acute setting only when severe pancreatitis is complicated by progressive jaundice or cholangitis.[28] Patients with gallstone pancreatitis should be considered for elective cholecystectomy after their pancreatitis resolves.

## Complications

The most common systemic complications are shock, renal failure, and respiratory insufficiency. Local complications include pancreatic necrosis with or without infection, as well as the development of pseudocysts.
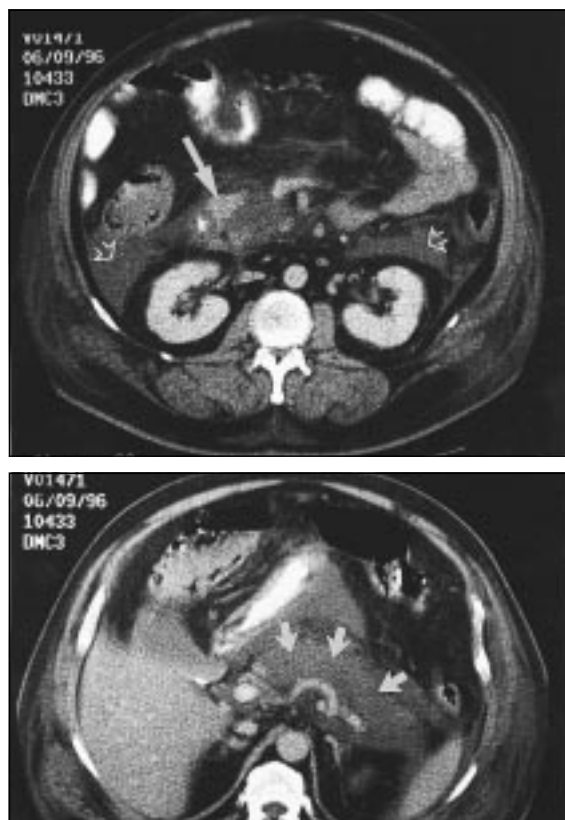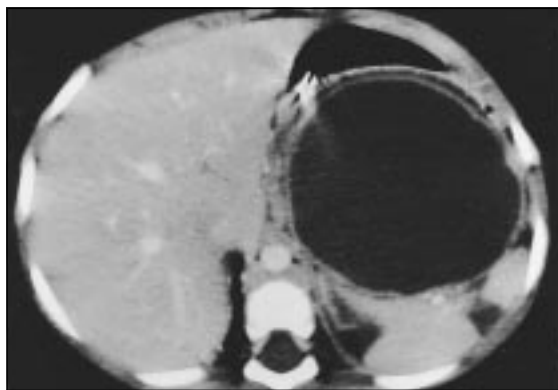
**Fig 5** Giant pseudocyst seen on computed tomography several weeks after an acute episode of pancreatitis

### Pancreatic necrosis

The lack of enhancement of pancreatic parenchyma on dynamic computed tomography indicates disruption of the microcirculation, hypoperfusion, and necrosis. If necrosis is detected but the patient improves, medical treatment is usually sufficient; patients who deteriorate need needle aspiration of pancreatic tissue for Gram stain and culture. If infected necrosis is present, early surgical debridement is necessary,[29] but early surgical debridement of sterile pancreatic necrosis is controversial and not widely used.

### Pseudocyst

A pseudocyst is a localised collection of pancreatic secretions that lacks an epithelial lining and persists for more than 4 weeks (fig 5).[6] Drainage should be considered if a pseudocyst enlarges beyond 5-6 cm diameter or causes pain or gastric outlet obstruction. Infection or haemorrhage involving a pseudocyst requires intervention. Surgical, percutaneous, and endoscopic drainage procedures have not been adequately compared in controlled trials. Percutaneous drainage is an effective method for decompression but may fail if the pseudocyst communicates with the main pancreatic duct.[30] Whenever a pseudocyst is drained the fluid obtained should be sent for Gram stain and culture.

Large pseudocysts adjacent to the stomach and to the duodenum can be drained by endoscopic cystogastrostomy and cystoenterostomy, respectively, with good results.[31] One or two double pigtail catheters are usually inserted into the cyst to assure drainage.

### Fistulas

Pancreatic fistulas are caused by disruption of the pancreatic duct and should be suspected in patients who develop massive ascites or pleural effusions.[7] Internal fistulas may communicate with the colon, small bowel, or biliary system or they may track to the skin as external fistulas. Fistulograms are usually sufficient to investigate external fistulas, but ERCP remains the test of choice for detecting internal pancreatic fistulas.[7] Surgery is required to treat persistent pancreatic fistulas.

## Aftercare

A follow up plan should be established so that patients with prolonged symptoms and late complications can be identified. While avoiding fat is important, a "100% fat free" diet is barely palatable and most patients will not eat it. Abstinence from alcohol (for at least several months) is mandatory. Patients with alcoholism need support. If oral narcotic analgesics are prescribed for use at home, the dose must be tapered to avoid long term dependence. Persistent pain and use of strong analgesics are warning signs which should prompt re-evaluation for possible complications. Failure to regain appetite and failure to regain weight are also important signs of continuing disease.

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